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World J Gastroenterol 2007 May 7; 13(17): 2496-2503
World Journal of Gastroenterology ISSN 1007-9327

BASIC RESEARCH

Relationship of quantitative structure and pharmacokinetics in fluoroquinolone antibacterials

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Received: 2007-01-10 Accepted: 2007-03-23

Abstract

AIM: To study the relationship between quantitative structure and pharmacokinetics (QSPkR) of fluoroquinolone antibacterials.

METHODS: The pharmacokinetic (PK) parameters of oral fluoroquinolones were collected from the literature. These pharmacokinetic data were averaged, 19 compounds were used as the training set, and 3 served as the test set. Genetic function approximation (GFA) module of Cerius^2 software was used in QSPkR analysis.

RESULTS: A small volume and large polarizability and surface area of substituents at C-7 contribute to a large area under the curve (AUC) for fluoroquinolones. Large polarizability and small volume of substituents at N-1 contribute to a long half life elimination.

CONCLUSION: QSPkR models can contribute to some fluoroquinolones antibacterials with excellent pharmacokinetic properties.

Key words: Quantitative structure pharmacokinetic relationship; Genetic function approximation; Fluoroquinolones; Elimination half life

Cheng D, Xu WR, Liu CX. Relationship of quantitative structure and pharmacokinetics in fluoroquinolone antibacterials. *World J Gastroenterol* 2007; 13(17):2496-2503

http://www.wjgnet.com/1007-9327/13/2496.asp

INTRODUCTION

H pylori is generally considered to be the most important cause of peptic ulcer diseases, gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach[1]. The widespread use of antibacterial therapy is suggested to be the cause for the decline in the prevalence of *H pylori* infection[2]. Among the different types of antibacterial agents, the effects of fluoroquinolones are better and have attracted much attention. Unfortunately, complete eradication of *H pylori* is still in the initial stage, especially in South East Asia and Southern Europe, where resistance to antibiotics has become more prevalent[3]. It is therefore important to search for better antibacterial agents against resistant *H pylori* strains[4].

Successful drugs must have suitable properties in toxicity, bioavailability and pharmacokinetic parameters. Screening of a large number of compounds with excellent absorption, distribution, metabolism, and excretion (ADME) properties is time-consuming and expensive[5]. So the extension of the idea of quantitative structure-activity relationship to the pharmacokinetics has led to the emergence of a new tool called the quantitative structure pharmacokinetic relationship (QSPkR) studies. QSPkR studies can be utilized at early stages of drug design. Both one- and two-dimensional topological indices have been used extensively to numerically relate molecular structure with activity[6]. These descriptors rely only on the molecular graph for their calculation. In contrast, three-dimensional descriptors require the absolute conformation of a molecule, and have been successfully used to develop QSPkR analysis[7].

The QSPkR models integrated properties of chemical structures (e.g. LogP) and their pharmacokinetic parameters (total clearance, distribution volume, *etc.*) of fluoroquinolones have been reported[8]. But these existing models cannot demonstrate the influence of the substituents to pharmacokinetic parameters. That is to say, these models can only predict pharmacokinetic parameters of the existing chemicals.

After examining the structures of all marketed fluoroquinolones, we found that their diversities in structures were mainly within R1 and R7 (Figure 1). Considering the connections between the groups (R1 and R7) and matrix were single bonds, the conjugations between groups and matrix were limited, and the groups had relatively independent properties. To simplify the design for high efficiency in practice, the properties of fragments were

applied as the descriptors of calculation. In this study, a two-step process was used to develop QSPkR models clinically using fluoroquinolone antibacterials. The first step was to calculate properties related to chemical structures and their conformation, especially constituent structures. These properties include 2D descriptors representing physical properties (logP), 3D descriptors (volume), and quantum chemical parameters (polarizability). After calculating these properties, the QSPkR models were developed by multivariate linear regression based on genetic algorithms.

Using these QSPkR models, we can illustrate how the changes at N-1 and C-7 of the fluoroquinolones affect their pharmacokinetic parameters. Hopefully, these QSPkR models can contribute to some fluoroquinolones with excellent pharmacokinetic properties.

MATERIALS AND METHODS

Molecules

All 22 compounds used in this study are analogues of the fluoroquinolone antibacterials which are widely used clinically except DW116 (No.5). The matrix of the compounds is shown in Figure 1, and their detailed substituents are listed in Figure 2.

Pharmacokinetic data

The PK parameters of these fluoroquinolones were collected from literature[9-68]. Data were taken from the studies of oral fluoroquinolones. These pharmacokinetic data were averaged after AUC and Cmax data were normalized by 100 mg of drugs (Table 1). $t_{1/2}$ in this paper is elimination half life, it is also known as $t_{1/2(\beta)}$. Nineteen compounds were used as the training set, and the others served as test set.

Molecular descriptors

The 3D structure of each compound was constructed by HyperChem 7.0 (Hypercube Inc., USA) and then optimized with MM+ force field. All molecules were aligned by minimizing the rms distance of their matrix by SYBYL 7.0 (Tripos Inc., 2004). The alignment of molecules is displayed in Figure 3. The descriptors were calculated for substituents R1 and R7 by HyperChem 7.0. The definitions of all descriptors are shown in Table 2.

QSPkR calculation

The logarithmic values of the PK parameters were used as the dependent variables. All the descriptors were scaled by the mean values of data from the training set .

The models related to three dependent variables [ln(AUC), $\ln(t_{1/2})$ and $\ln(C_{max})$] and 14 independent variables were built respectively according to the data of the training set. To obtain a high quality of QSPkR models, genetic algorithms (GA) and partial least squares analysis (PLS) were used in calculation. The calculation was conducted with the QSAR module of Cerius^2 (Accelrys Software Inc.) molecular modeling software.

We selected three and four independent variables to search their best models. QSPkR analysis based on GA began with a population of random models. These models

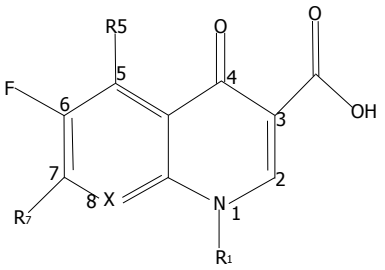


Figure 1 The matrix of all fluoroquinolone antibacterials.

were generated by randomly selecting three or four features from the data file. Product of multiple linear regression coefficient and leave-one-out cross-validation coefficient was used as a fitness function to generate the fitness scores of these models. For this data set 200 populations were used, and the number of elite populations was 100. The genetic operator was applied until the total fitness score of the elite populations could not be improved over a period of 30 crossover operations. The convergence criteria was met after 430 operations for four features and 280 operations for three features.

The parameters like correlation coefficient (R), variance ratio (F), lack of fit (LOF) scores and leave-one-out cross-validation coefficient (S) were also computed for the suitability of fitness.

The data of the left test set were then predicted by these models.

RESULTS

Calculation of descriptors

The descriptors were calculated for substituents R1 and R7 by HyperChem 7.0. And their values are displayed in Tables 3 and 4.

Fitted models

The GA calculation gave 100 models for each pharmacokinetic parameter. The models with the best fitness are listed in Table 5. Results showed that GA was a powerful tool to find the best models. Maximum R^2 of models based on ln(Cmax) was only 0.327. Therefore, these models might not be significant. That is to say these 14 descriptors were not correlated with Cmax.

All the predicted and observed data of ln(AUC) and $\ln(t_{1/2})$ from the training set are displayed in Figure 4.

DISCUSSION

We normalized the data of all the descriptors before model construction, making the coefficient of all the descriptors comparable in the same model. In the model based on AUC, coefficient of V7 was the largest and negative, and that of HE7 was quite small, suggesting that the substituents at position 7 are very significant to AUC, and small volume, large polarizability and large surface area substituents at C-7 are preferred, while hydration energy has little influence on AUC.

In fact, compounds with relatively small volume and large polarizability and surface area of substituents at C-7

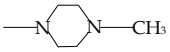
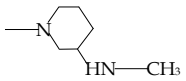
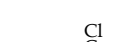
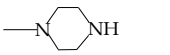
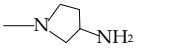
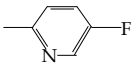
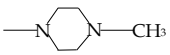
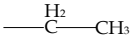
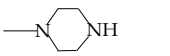
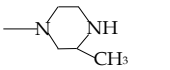
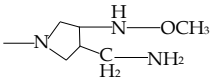
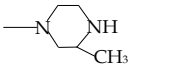
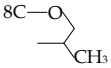
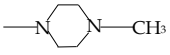
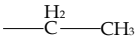
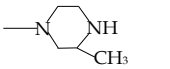
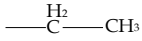
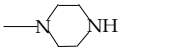
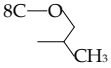
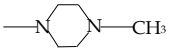
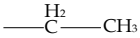
Compounds No.	Name	R1	R5	R7	X
1	Amifloxacin		—H		
2	Balofloxacin		—H		
3	Ciprofloxacin		—H		
4	Clinafloxacin		—H		
5	DW116		—H		
6	Enoxacin		—H		
7	Gatifloxacin		—H		
8	Gemifloxacin		—H		
9	Grepafloxacin		—CH_3		
10	Levofloxacin		—H		
11	Lomefloxacin		—H		
12	Norfloxacin		—H		
13	Ofloxacin		—H		
14	Pefloxacin		—H		
15	Rufloxacin		—H		
16	Sitafloxacin		—H		
17	Sparfloxacin		—NH_2—		
18	Temafloxacin		—H		
19	Trovafloxacin		—H		
20	Difloxacin		—H		
21	Fleroxacin		—H		
22	Tosufloxacin		—H		

Figure 2 The substituents of fluoroquinolone antibacterials.

(Table 4) all had relatively large AUC (Table 1). Although compounds 3, 4, 12 and 22 (Table 4) had substituents at C-7 with very small volume, their AUCs were all small(Table 1) because of extremely small polarizability and surface area (Table 4), suggesting that coefficient of V7 is not the definitive factor to affect AUC. Volume, polarizability and surface area of R7 determined AUC, and small volume, large polarizability and large surface area of substituents at C-7 were of benefit to large AUC. It is coincident with the results of coefficients in the AUC-based model.

In the $t_{1/2}$-based model, coefficient of V1 was the

Table 1 Pharmacokinetic data of fluoroquinolones from human studies

Compounds		PK parameters						References
		[1]$AUC_{0-\infty}$ (μg·h/mL)		[1]$t_{1/2}$ (h)		[1]Cmax (mg/L)		
No.	Name	Range	Average	Range	Average	Range	Average	
				Training set				
1	Amifloxacin	5.5-5.62	5.57	3.58-4.83	4.14	0.9-1.26	1.14	9, 10
2	Balofloxacin	8.55	8.55	7.8	7.8	1.08	1.08	11
3	Ciprofloxacin	2.12-3.53	2.56	3.01-4.7	4.16	0.4-0.69	0.56	12-15
4	Clinafloxacin	4.63-5.93	5.34	5.09-6.13	5.74	0.6-0.84	0.72	16-18
5	DW116	18.54-23.3	21.86	14.53-18.7	15.82	1.1-1.22	1.17	19
6	Enoxacin	2.9-5.47	4.36	2.35-4.98	3.54	0.62-0.81	0.66	20-22
7	Gatifloxacin	6.5-8.92	7.87	6.52-8.6	7.46	0.84-1.03	0.9	23-26
8	Gemifloxacin	2.79-3.43	3.02	5.87-8.2	6.65	0.46-0.73	0.56	27-29
9	Grepafloxacin	2.83-4.05	3.43	9.2-12.7	11.53	0.24-0.41	0.32	11, 12, 30, 31
10	Levofloxacin	8.96-9.5	9.33	6-7.4	6.78	0.16-0.3	0.24	32-34
11	Lomefloxacin	8.05-13.53	9.84	5.5-12.7	7.73	0.95-1.18	1.06	35-37
12	Norfloxacin	1.7-1.85	1.77	3.5-4.02	3.7	0.32-0.36	0.33	38-40
13	Ofloxacin	6.68-11.64	7.67	4.6-6.7	5.32	0.71-1.33	0.87	41-45
14	Pefloxacin	24.4-40.78	29.97	10.9-15.06	14.63	1.03-1.68	1.44	46-48
15	Rufloxacin	35.8-44.03	39.43	28.2-40	34.25	0.68-1.13	0.99	49-52
16	Sitafloxacin	5.62-6.02	5.88	4.6-7	5.4	0.9-0.93	0.92	53-54
17	Sparfloxacin	8.08-11.96	8.35	16.5-25.56	20.06	0.23-0.4	0.34	55-57
18	Temafloxacin	7.42-10.63	8.45	7.8-10.6	8.55	0.61-0.9	0.74	58-60
19	Trovafloxacin	9.75-14.47	11.91	7.8-10.8	9.66	0.97-1.5	1.23	61-63
				Test set				
20	Difloxacin	26.6-28.3	27.8	20.6-28.8	25.7	1.02-1.1	1.04	64
21	Fleroxacin	16.3-20.65	18.13	7.9-13	11.02	1.19-1.58	1.4	32, 65, 66
22	Tosufloxacin	1.49-3.3	2.62	3.6-4.85	4.02	0.21-0.4	0.34	67-69

[1]$AUC_{0-\infty}$ is area under the plasma concentration-time curve from time zero to infinity; $t_{1/2}$ is elimination half life; Cmax is maximum concentration of the drug in plasma.

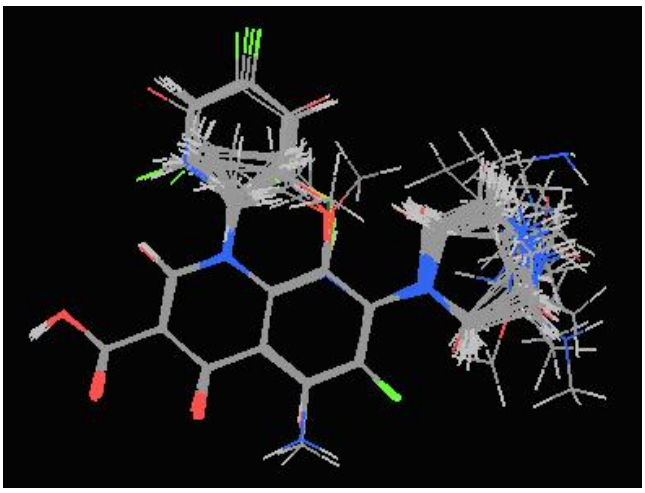


Figure 3 The alignment of fluoroquinolone molecules.

Table 2 Descriptors used in this paper

Descriptors	Physicochemical meaning
SA7	Surface area (grid) of R7
V7	Volume of R7
HE7	Hydration energy of R7
LP7	Logp of R7
RF7	Refractivity of R7
P7	Polarizability of R7
MW7	Molecular weight of R7
SA1	Surface area (grid) of R1
V1	Volume of R1
HE1	Hydration energy of R1
LP1	Logp of R1
RF1	Refractivity of R1
P1	Polarizability of R1
MW1	Molecular weight of R1

largest and negative, but that of P7 and HE7 was quite small, suggesting that the substituents at position 1 are significant to $t_{1/2}$, large polarizability and small volume of substituents at N-1 are therefore preferred.

In fact, compounds with relatively small volume and large polarizability of substituents at N-1 (Table 4) all had relatively large $t_{1/2}$ (Table 1). Compounds 1, 6, 11 and 12 with very small volume of substituents at N-1(Table 4) had small $t_{1/2}$ (Table 1) because of extremely small polarizability (Table 4), and compounds 18, 19 and 22 with extremely large polarizability of substituents at N-1 (Table 4) had relatively small $t_{1/2}$ (Table 1) because of too large volumes. Therefore, volume and polarizability of R1 determine $t_{1/2}$ and small volume and large polarizability of substituents are beneficial to large $t_{1/2}$. It is coincident with the coefficients in the $t_{1/2}$-based model.

Predicted data for test set

The AUC and $t_{1/2}$ data of test set (Table 6) were predicted by models displayed in Table 5.

The ln(AUC) values predicted by the model correlated well with the observed ln(AUC) values for the training data set with correlation coefficient (R2) equal to 0.7369 (Figure 4A). In addition, application of the model to an external test data set consisting of 3 compounds demonstrated

Table 3 Descriptors for group R7 of all fluoroquinolones compounds

No.	R7						
	SA7	V7	HE7	LP7	RF7	P7	MW7
1	271.21	398.4	5.48	-0.36	27.44	11.56	99.16
2	299.04	445.86	5.04	-0.15	31.33	13.39	113.18
3	247.54	347.95	1.46	-0.72	22.15	9.72	85.13
4	248.59	344.96	0.9	-1	21.91	9.72	85.13
5	266.41	382.26	5.33	-0.36	27.44	11.56	99.16
6	251.07	350.09	1.58	-0.72	22.15	9.72	85.13
7	265.94	383.08	3.5	-0.31	26.57	11.56	99.16
8	300	442.55	-2.21	-0.28	35.48	14.96	142.18
9	261.99	381	3.58	-0.31	26.57	11.56	99.16
10	264.36	391.96	5.45	-0.36	27.44	11.56	99.16
11	260.22	378.35	3.68	-0.31	26.57	11.56	99.16
12	250.06	350.92	1.37	-0.72	22.15	9.72	85.13
13	269.89	397.69	5.39	-0.36	27.44	11.56	99.16
14	258.05	374.48	5.68	-0.36	27.44	11.56	99.16
15	258.5	378.79	5.73	-0.36	27.44	11.56	99.16
16	281.66	422.58	3	-0.4	28.87	12.62	111.17
17	298.38	442.76	5.55	0.11	30.99	13.39	113.18
18	266.8	385.12	3.43	-0.31	26.57	11.56	99.16
19	244.47	346.87	4.31	-1.24	24.6	10.78	97.14
20	260.91	378.28	5.31	-0.36	27.44	11.56	99.16
21	264	387.29	5.61	-0.36	27.44	11.56	99.16
22	231.53	320.13	2.75	-1	21.91	9.72	85.13

Table 4 Descriptors for group R1 of all fluoroquinolones compounds

No.	R1						
	SA1	V1	HE1	LP1	RF1	P1	MW1
1	162.65	191.65	-4.39	-0.41	6.5	3.64	30.05
2	184.12	230.99	2.6	1.13	10.1	5.41	41.07
3	183.13	229.07	2.59	1.13	10.1	5.41	41.07
4	181.83	225.71	2.61	1.13	10.1	5.41	41.07
5	232.61	320.17	-3.57	1.43	24.71	9.18	96.08
6	171.57	206.82	0.73	1.32	7.29	4.35	29.06
7	192.14	241.82	2.56	1.13	10.1	5.41	41.07
8	180.91	225.56	2.61	1.13	10.1	5.41	41.07
9	185.87	233.6	2.57	1.13	10.1	5.41	41.07
10	209.76	274.58	0.58	2.4	13.05	6.37	58.08
11	173.79	211.56	0.71	1.32	7.29	4.35	29.06
12	172.99	213.28	0.7	1.32	7.29	4.35	29.06
13	213.93	278.93	0.71	2.4	13.05	6.37	58.08
14	172.31	210.04	0.72	1.32	7.29	4.35	29.06
15	187.74	241.74	-1.24	0.8	15.93	7.69	60.11
16	194.84	249.45	2.6	0.82	9.92	5.32	59.06
17	193.09	243.16	2.55	1.13	10.1	5.41	41.07
18	246.11	343.09	-3.4	2.14	26.43	9.8	113.09
19	246.34	343.09	-3.4	2.14	26.43	9.8	113.09
20	239.88	334.78	-2.47	2	26.21	9.89	95.1
21	168.2	205.76	0.8	0.92	7.37	4.26	47.05
22	248.12	343.14	-3.4	2.14	26.43	9.8	113.09

that the model-predicted AUC values were approximate to the observed AUC values (Table 6), indicating that the constructed model is valid for AUC.

The $\ln(t_{1/2})$ values predicted by the model also correlated well with the observed $\ln(t_{1/2})$ values for the training data set with correlation coefficient (R2) equal to 0.7287 (Figure 4B). In addition, the model-predicted $t_{1/2}$ values were approximate to the observed $t_{1/2}$ values (Table 6), indicating that the constructed model is also valid for $t_{1/2}$.

These models may be used to predict the pharmacokinetic parameters (AUC and $t_{1/2}$) of untried fluoroquinolones. But residual values between predicted and observed data of the test set are slightly larger especially for AUC. It is mainly due to non-precise pharmacokinetic data. Although all the pharmacokinetic data obtained from the literature were averaged, they were not precise enough to get excellent models. The other reason is that we only considered diversities within R1 and R7 to simplify the models. These models however, are very useful as in-silicon prefilters of

Table 5 QSPkR models from the training set data

No.	Model	R^2	R	F	S	LOF
AUC	ln(AUC) = 2.27895 + 1.22614 (HE7) + 9.96141 (P7) - 20.5953 (V7) + 9.13637 (SA7)	0.737	0.858	9.801	0.550	0.472
$t_{1/2}$	ln($t_{1/2}$) = 1.49842 + 1.80503 (P7) + 0.492241 (HE7) - 5.26324 (V1) + 3.53476 (P1)	0.729	0.854	9.400	0.555	0.280
Cmax	ln(Cmax) = 2.96161 - 5.92537 (V1) + 2.15698 (MW1) + 0.206369 (P7) + 0.26873 (HE7)	0.327	0.572	1.697	-0.093	0.523

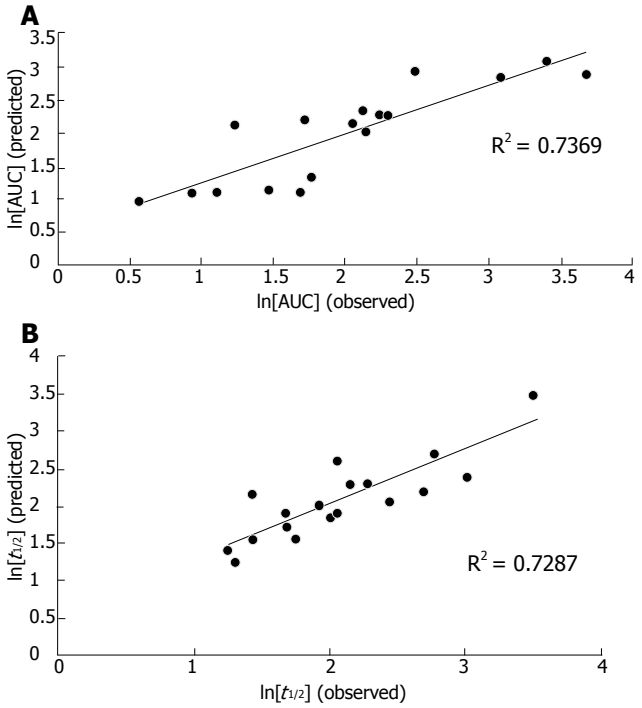


Figure 4 The comparison of the predicted and observed ln(AUC) (**A**) and ln($t_{1/2}$) (**B**).

Table 6 Predicted and observed data of the compounds in the test set

Compounds	Observed		Predicted	
	AUC	$t_{1/2}$	AUC	$t_{1/2}$
20	27.8	25.7	17.431	16.395
21	18.13	11.02	13.269	9.388
22	2.62	4.02	12.034	6.852

fluoroquinolone compounds in virtual high throughput screening. And qualitative analysis of substituents at N-1 and C-7 may contribute to guide design of novel fluoroquinolones with excellent pharmacokinetic properties

In conclusion, this model can contribute to a series of fluoroquinolone antibacterial drugs with excellent pharmacokinetic properties for complete eradication of *H pylori*.

ACKNOWLEDGMENTS

We thank Shandong University (Shandong, China) for allowing us to use the Cerius^2 molecular modeling software (Accelrys) and Hypercube Inc. for providing us HyperChem 7.0 Evaluation for Windows (download from http://www.hyper.com/).

COMMENTS

Background

Successful drugs must have suitable properties in toxicity, bioavailability and pharmacokinetic parameters. Screening for a large number of compounds with excellent absorption, distribution, metabolism, and excretion (ADME) properties is time-consuming and expensive. So the extension of the idea of quantitative structure-activity relationship (QSAR) to pharmacokinetic data has led to emergence of new tool called quantitative structure pharmacokinetic relationship (QSPkR) study. QSPkR study can be utilized in drug design.

Research frontiers

Both one- and two-dimensional topological indices have been used extensively to numerically relate molecular structure with activity and/or property. (These descriptors rely only on the molecular graph for their calculation. In contrast, three-dimensional descriptors require the absolute conformation of a molecule. They, too, have been successfully used to develop QSPkRs.

Innovations and breakthroughs

In this study the authors have developed and demonstrated novel computational approaches for the efficient and accurate prediction of AUC and $t_{1/2}$ of fluoroquinolones. They constructed simple models which can directly correlate physical and chemical properties to pharmacokinetic data. These models can be used not only to predict pharmacokinetic parameters but also to guide the design of novel fluoroquinolones.

Applications

Using these QSPkR models, the authors can illustrate how the changes at N-1 and C-7 of the fluoroquinolones affect their pharmacokinetic parameters. Such computational models may be useful as in-silico prefilters of fluoroquinolones compounds in a virtual high throughput screening environment and as a research tool for identifying and improving the pharmacokinetic profiles of fluoroquinolones candidates.

Peer review

In the present study, the authors have tried to develop computational approaches for the prediction of the pharmacokinetics of fluoroquinolones. Quantitative structure-pharmacokinetics relationship analysis can be an important tool at the early stage of drug design. The authors demonstrated that small volume and large polarizability of substitutents of R-1 are beneficial to large $t_{1/2}$ and small volume, large polarizability and surface area of substitutents at C-7 are of benefit to large AUC in fluoroquinolones.

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